Introducing LATE: An important underpinning of dementia in later life

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He has also served on advisory board for Eisai.
Outline

• Introduction and historical background

• Introducing Limbic predominant age related TDP-43 encephalopathy (LATE)

• Cognitive impact of LATE
From Pyramid to Pillar: A Century of Change
Population of the United States

1960
Ages
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
Millions of people

2060

Source: National Population Projections, 2017
www.census.gov/programs-surveys/popest/
Projections for Alzheimer’s disease

- Alzheimer’s disease and related dementia (ADRD) are the health care tsunamis of the 21st century
- The oldest old are the fastest growing segment with highest rates of dementia
Evolution of dementia nosology

- **1970s**: Hardening of arteries
- **1980s**: Alzheimer's disease -> Multi-infarct dementia
- **1990s**: Alzheimer's disease -> Vascular dementia -> Dementia with Lewy bodies
- **2000s**: Alzheimer's disease -> Vascular dementia -> Dementia with Lewy bodies -> Frontotemporal dementia
- **2010s**: Alzheimer's disease -> Vascular dementia -> Dementia with Lewy bodies -> Frontotemporal dementia -> CTE -> Hippocampal sclerosis -> LATE
Etiology of Alzheimer’s dementia

- Disconnect between Alzheimer’s clinical syndrome and Alzheimer’s pathology

TDP-43
TDP-43

- TransActive Response (TAR) DNA binding protein of 43 kDa
- Ubiquitously present in all cell nuclei
- Regulator of gene expression
- Bad when it gets trapped in cytoplasm
Frontotemporal dementia
- Primary tauopathy
- TDP-43

Alzheimer’s dementia
- Amyloid β plaques
- Tau tangle
- TDP-43

Hippocampal sclerosis
- TDP-43
- Arteriolo-sclerosis
TDP-43 and dementia syndromes

Frontotemporal dementia: 50-60 years
Alzheimer’s disease: 70-80 years
Hippocampal sclerosis: > 85 years
Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson, 1, Dennis W. Dickson, 2, John Q. Trojanowski, 3, Clifford R. Jack Jr., 4, Patricia A. Boyle, 5, Konstantinos Arfanakis, 5, 6, Rosa Rademakers, 2, Irina Alafuzoff, 7, Johannes Attenu, 8, Carol Brayne, 9, Ian T.S. Coyle-Gilchrist, 9, Helena C. Chui, 10, David W. Fardo, 1, Margaret E. Flanagan, 11, Glenda Halliday, 12, Suvi R.K. Hokkanen, 9, Sally Hunter, 9, Gregory A. Jicha, 1, Yuriko Katsumata, 1, Claudia H. Kawas, 13, C. Dirk Keene, 14, Gabor G. Kovacs, 15, Walter A. Kukull, 14, Allan I. Levey, 16, Nazanin Makkinejad, 6, Thomas J. Montine, 17, Shigeo Murayama, 18, Melissa E. Murray, 2, Sukriti Narg, 5, Robert A. Rissman, 19, William W. Seeley, 20, Reisa A. Sperling, 21, Charles L. White III, 22, Lei Yu 5, and Julie A. Schneider 5
LATE-NC

- TDP-43 pathology in limbic structures in those > 85 y/o
  - Present in > 30% of autopsied brains
  - Associated with an amnestic syndrome
  - Clinically diagnosed as Alzheimer’s during life

- 4 stages:
  - Stage 0: no TDP-43 pathology
  - Stage 1: confined to amygdala
  - Stage 2: spread to hippocampus
  - Stage 3: involvement of middle frontal gyrus

Nelson et al. Brain, 2019
Nelson et al. Acta Neuropathological 2022
<table>
<thead>
<tr>
<th>The 90+ Study</th>
<th>NACC</th>
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<tbody>
<tr>
<td>• Community based cohort in Southern California</td>
<td>• National database of Alzheimer’s disease research centers (ADRC)</td>
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<tr>
<td>• Longitudinal assessments</td>
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<tr>
<td>• High autopsy rates</td>
<td>• High number of participants</td>
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<td>• Available biomarkers</td>
<td>• Uniform pathology dataset</td>
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## Demographics

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<tr>
<td></td>
<td>LATE-NC (N=149, 36%)</td>
</tr>
<tr>
<td>Age at Death (Mean (SD))</td>
<td>98 (± 3.7)</td>
</tr>
<tr>
<td>Female</td>
<td>104 (69.8%)</td>
</tr>
<tr>
<td>College or More education</td>
<td>79 (53.0%)</td>
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<tr>
<td>Dementia</td>
<td>90 (60.4%)</td>
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## Demographics

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<th>The 90+ Study</th>
<th>NACC (&gt;90 years old)</th>
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<tr>
<td></td>
<td>LATE-NC (N=149, 36%)</td>
<td>Other (N=258, 64%)</td>
</tr>
<tr>
<td>Age at Death (Mean (SD))</td>
<td>98 (± 3.7)</td>
<td>97 (± 3.5)</td>
</tr>
<tr>
<td>Female</td>
<td>104 (69.8%)</td>
<td>178 (69.0%)</td>
</tr>
<tr>
<td>College or More education</td>
<td>79 (53.0%)</td>
<td>127 (49.2%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>90 (60.4%)</td>
<td>88 (34.1%)</td>
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<tr>
<td></td>
<td>LATE-NC (N=144, 41%)</td>
<td>Other (N=203, 59%)</td>
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<td>94 (± 3.7)</td>
<td>94 (± 3.5)</td>
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<tr>
<td></td>
<td>83 (57.6%)</td>
<td>116 (57.1%)</td>
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<td>113 (78.5%)</td>
<td>103 (50.7%)</td>
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Is LATE related to dementia and clinical Alzheimer’s?

![Graph showing clinical manifestation of Dementia and Clinical AD across different cohorts.][1]

Unpublished
How is LATE related to other pathologies?
Relationship with cognitive domains (The 90+ Study)
Comparison with Alzheimer’s pathology

- LATE-NC
- ADNC

Graph showing comparison of dementia, memory, language, orientation, executive function, and visuospatial function between LATE-NC and ADNC.
## LATE-NC in the full NACC cohort

<table>
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<tr>
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<th>LATE-NC (N=508, 32%)</th>
<th>Other (N=1083, 68%)</th>
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<tbody>
<tr>
<td><strong>Age at Death (Mean (SD))</strong></td>
<td>84 (± 9.5)</td>
<td>78 (± 12)</td>
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<tr>
<td><strong>Female</strong></td>
<td>259 (51.0%)</td>
<td>490 (45.2%)</td>
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<tr>
<td><strong>Education years (Mean (SD))</strong></td>
<td>16 (± 3.0)</td>
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</tr>
<tr>
<td><strong>Dementia</strong></td>
<td>451 (88.8%)</td>
<td>820 (75.7%)</td>
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Associations by stages of LATE-NC (NACC)
Conclusion

• LATE-NC is a common degenerative pathology

• LATE-NC is related to dementia and impairment in cognitive domains

• Its cognitive signature is very similar to Alzheimer’s disease pathology

• It remains a postmortem diagnosis
Acknowledgement

• The 90+ Study
  Claudia Kawas
  Maria Corrada
  Natalie Bryant

• Sajjadi Lab
  Davis Woodworth
  Katelynn Nguyen
  Anne-Marie Leiby
  Hannah Nguyen
  Kiana Scambray

• Stanford Team
  Thomas Montine
  Syed Bukhari

NIH National Institute on Aging
R01AG21055; PI: Kawas, Corrada
R01AG062706; PI: Sajjadi
Thank you

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LATE stages results

Clinical Symptoms
- Dementia
- Clinical AD

Related Pathologies
- HS
- ADNC
- Lewy Bodies

Global Vascular Pathologies
- Atherosclerosis
- Arteriolosclerosis

Stage
- LATE-NC Stage 1
- LATE-NC Stage 2
- LATE-NC Stage 3